REMARKS/ARGUMENTS

As this is in response to the Final Rejection dated June 10, 2003, Applicant respectfully requests a one-month extension of time for submitting this Amendment.

The undersigned acknowledges with appreciation the telephone interview with Examiners Nichols and Kemmerer held on September 15, 2003 and for the courtesies extended by the Examiners. During the interview, at which Mark Halvorson of this firm was also present, the Final Rejection of the application was discussed along with proposed amendments to the claims which are being made herein.

At the telephone interview, the undersigned reviewed the background of the invention, pointing out that Dr. Wayne Franco, the applicant herein, had done the early work on the treatment of heart disease by the use of human growth factor protein FGF; this was evidenced in U.S. Patent 4,296,100 to Dr. Franco which was cited in the Final Rejection (and is also referred to in the instant specification). It was pointed out that the claims that were rejected are directed to a multi-tiered treatment method and that there was sufficient support in the specification (particularly for human growth factor proteins FGF-1, FGF-2, VEGF and mixtures thereof) for the use of such proteins in the claimed process to enable one skilled in the art to make and use the invention. It was also pointed out that potential side effects should not bear on the issue of enablement, as these types of issues were within the purview of the FDA rather than the Patent and Trademark Office. It was also mentioned that treatment of heart disease via intracoronary injection was known from the Franco U.S. patent 4,296,100 and that there was sufficient evidence in the specification (e.g., Example 8) regarding dosages for inhalation therapy.

It was also pointed out that inhalation therapy had been suggested for other proteins, such as insulin and interferon, which have similar particle sizes to the human growth factor proteins of this application based on their molecular weight. It was further mentioned that the dilution factor for insulin by inhalation disclosed in U.S. Patent 5,915,378 to Lloyd et al. (which was already of record) and that one skilled in the art would understand that applying a similar dilution for the proteins of this

invention would result in an effective treatment, using the dosage levels disclosed in Example 8 and in view of the dosage levels identified in U.S. Patent 4,296,100 to Franco. It was submitted in summary that one skilled in the art would not have to undertake undue experimentation to practice the invention.

Examiner Nichols stated that there were two basic grounds for the rejection. The first was that the claims were perceived as too broad for the disclosure, but if the specific proteins of dependent claims 20 and 40 would be recited in independent claims 16 and 35, this would obviate that ground of objection. The Examiner is thanked for his helpful suggestions, which have been implemented by the foregoing amendments to the claims. The second basis for the rejection was whether the delivery by inhalation therapy of these growth factor proteins was effective to treat coronary disease.

As to the second point, the undersigned pointed out that the PTO agreed in the Final Rejection that these proteins would reach the heart via inhalation and that the dosages were set forth in the specification. It was also pointed out that it had been established that these proteins could be administered intravenously, a systemic delivery rather than the localized delivery effected by inhalation, and that other proteins (as mentioned above) also have been delivered by inhalation.

The Examiners stated that if the claims were so amended and the arguments presented, they would give favorable consideration to the application. Examiner Kemmerer also asked whether a post-filing literature search could be done for inhalation therapy of these growth factor proteins and the undersigned stated that he would have such a search conducted.

Turning now to the proposed amendments to the claims, independent claims 16 and 35 have been amended to incorporate the features of dependent claims 20 and 40, respectively, and claims 20 and 40 have accordingly been canceled. Non-elected claims 25-34 have been canceled to advance the prosecution of the application, with the right to re-submit the same in a divisional application. Previously pending claim

47 has been canceled also to advance the prosecution. Other claims were amended to delete reference to "New" that was discussed in the first Office Action.

New claims 54 to 61 have been added to recite specific features of Applicant's invention. Claims 54 and 56 recite that the growth factor protein formulations comprise FGF-1 and/or FGF-2. Claims 55 and 57 recite that the growth factor protein formulations comprise VEGF. Claims 58 and 59 recite that the formulation is a dry powder or liquid aerosol, respectively, as previously claimed in claims 26 and 27. Claim 60 recites that the acute symptom of heart disease is reperfusion injury, which was part of canceled claim 31. Claim 61 is similar to canceled claim 32.

Upon entry of this Amendment, the claims now presented are claims 16-19, 21-24, 35-39, 41-43 and 54-61. It is respectfully submitted that these claims are patentable and should be allowed.

In the Final Rejection, claims 16-24, 35-43 and 47 were rejected under 35 USC 112 ¶1, and claim 47 was also rejected under 35 USC 112 ¶2. Claim 47 has been cancelled to advance the prosecution and hence the rejections of that claim are no longer an issue. It is submitted that with the amendments to the claims set forth above, all of the pending claims fully comply with the enablement requirement of 35 USC 112 ¶1.

The detailed review of this application by Examiner Nichols is appreciated. Based on the discussion at the telephone interview and in view of the amendments made to the claims, it is believed that it is not necessary in this paper to respond to each and every point made in the Final Rejection; rather, it would be more helpful to discuss the patentable nature of the pending claims in response to the issues raised by the Examiners.

The invention is directed to a method for the systematic, multi-tiered treatment of coronary artery disease, by delivery of a formulation comprising a growth factor protein. The growth factor protein is selected from the group of FGF-1, FGF-2, VEGF and mixtures thereof. The growth factor protein is administered by inhalation

therapy. Next, one or more clinical indicators of coronary artery disease is monitored. After that, it is determined whether an additional dose of a growth factor protein formulation is needed, and depending on such results, one or more additional dosages of a second growth factor protein formulation is administered preferably by a method of delivery more invasive than inhalation therapy. These latter steps are repeated until there is a clinical indication of amelioration of the symptoms or until there is a contraindication to continued treatment. Dependent claims set forth further features of Applicant's invention.

It is respectfully submitted that one having skill in the art would understand how to make and use the invention as claimed in the pending claims. The instant specification is replete with reference to treatment of coronary artery disease by FGF-1, FGF-2 and VEGF. Page after page starting with page 16 of the specification are devoted to the pulmonary route of administration. There are many citations to technical articles and patent literature which are directed to inhalation therapy and the advantages thereof. The mechanism of absorption is discussed (see, e.g., page 19 of the specification), as is the method of formulation (see, e.g., page 21 of the specification). Likewise, the specification is replete with references to the multi-tiered approach claimed herein. Example 8 starting at page 79 is directed to the administration of proteins by oral inhalation and sets forth dosage levels for FGF and VEGF. Also discussed are dosing schedules.

It is submitted as being clear that independent claims 16 and 35, which are now directed to specific growth factor protein formulations (i.e., FGF-1, FGF-2 and VEGF), as well as their dependent claims, find more than adequate support in the specification so that the claims are not unduly broad. Furthermore, these claims clearly enable one skilled in the art how to make and use the claimed invention.

There was much discussion in the Final Rejection of allegedly possible side effects based on the treatment by inhalation therapy. It is respectfully pointed out that it is well settled that the safety of administering a medication and the like should not form the basis of a rejection by the Patent and Trademark Office; rather, this is within

the purview of the Food and Drug Administration. See, for example, *In re Brana et al.*, 51 F3d 1560 (34 USPQ 2d 1436), CAFC 1995.

In further response to the points mentioned in the Final Rejection, it is submitted that treatment of coronary artery disease by growth factor proteins is known – see Franco, USP 4,296,100. The method of administration in the Franco patent is by direct injection into the heart or by intravenous injection. As mentioned in the Final Rejection at page 5, Dr. Franco's earlier patent specifies that FGF is biologically active at low dosages such as 1 to 10 nanograms or 25 to 200 nanograms. His prior patent also specifies dosages for IC delivery – see, e.g., claims 4-6. In the Final Rejection (page 5) it is recognized that the claimed growth factor proteins would reach the heart by the claimed method.

In addition, the delivery by IV of these growth factor proteins is also discussed in the instant specification (see, e.g., paragraph [0006] at page 4) as well as in U.S.P. 6,440, 934 to Whitehouse (of record) - see, e.g., col. 14, line 30 et seq. If delivery by such a technique, which is systemic since it requires passage through the circulatory system, is effective, it is clear that one skilled in the art would recognize from the invention claimed herein that pulmonary delivery, which is localized, would also be effective. Indeed, the instant specification discusses that the dosage for inhalation therapy is similar as for intracoronary delivery (see, e.g., Example 8).

The mechanism for delivery of the claimed growth factor proteins is fully discussed in the present specification – see, e.g., paragraph [0027] at page 12 and paragraphs [0039-0043] at page 16 et seq.

It is also pointed out that delivery by inhalation therapy of other proteins of similar particle size is known to be an effective delivery mechanism. For example, inhalation delivery of insulin is discussed starting at paragraph [0044], page 18 of the specification. Paragraph [0045] discloses the administration of lutenizing hormone-releasing hormone (LHRH), a decapeptide, and Paragraph [0046] discusses the bioavailability of LHRH as well as interferon-α.

The Patton article of record, at page 15, recites in Table 2 the particle size of various molecules, based on their molecular weight. It can be seen that insulin has a particle size diameter of between about 2.2-2.6 nm, with a molecular weight of 5700. The proteins used in the present invention have molecular weights in the range of about 15,000 to 20,000, which based upon Table 2 of Patton would mean that the particle size would be between about 3.0 to 3.8 nm (based on the molecular weights of cytochrome c and myoglobin given in that table). This particle size range is very close to that of insulin.

In addition to the bioavailability disclosure of the instant specification, the Lloyd et al. patent of record (USP 5,915,378) is directed to creating an aerosolized formulation of insulin, and discusses at col. 40, line 44 et seq., that by inhalation as little as 10% or as much as 50% of the amount delivered by an intrapulmonary method may actually reach the circulatory system of the patient. It is respectfully submitted that one skilled in the art, knowing that insulin can effectively be delivered by inhalation therapy, would be enabled by Applicant's teaching of inhalation therapy of the claimed growth factor proteins without undue experimentation, since they are all proteins of similar particle size. The inhalation dosages are disclosed in the instant specification and it is clear from the Franco patent (as recognized in the Final Rejection) that only very small amounts of these proteins are effective to treat coronary artery disease by intracoronary treatment. Given that the dilution factors are established by, e.g., Lloyd et al., for another protein (insulin), one skilled in the art would recognized, without undue experimentation, that the claimed method could be effectively practiced.

With more specific reference to the dilution factor, Whitehouse discloses delivering FGF protein by IV at dosages of 0.02 to 48 μg/ kg of patient (see, e.g., col. 2, line 51 et seq.). Parenthetically, it is noted that the instant specification teaches that the efficiency of delivery by inhalation would be higher than for IV (see Example 8).

Assuming an average patient weighs about 70 kg, then the absolute dosage of Whitehouse ranges from 1.4 μg to 3.4 mg. The Franco patent discloses delivering FGF protein by IC or IV at dosages of 10 μg to 1 g/ 100 g of heart. Assuming an

average male heart weighs about 300 grams, then the absolute dosage from this teaching is 60 μg to 6 g.

Lloyd et al. disclose that the dilution factor of insulin administered by inhalation is approximately 10 to 50% effective in reaching the circulatory system. For this discussion, let's assume the lowest amount (10%).

In Example 8 of the application, the dosages for FGF by inhalation are disclosed as from 10 μg to 20 mg, and dosages for VEGF are from 10 μg to 10 mg. Based on a dilution factor of 10%, and assuming administering the highest dosage set forth in Example 8, then 2 mg of FGF and 1 mg of VEGF would reach the circulatory system. This is clearly within the range of dosages shown to be effective in both Whitehouse and Franco, and the delivery of these proteins by inhalation would go directly to the heart before entering the entire circulatory system.

Even if one were to use a dilution factor which is an order of magnitude lower than the dilution factor disclosed in Lloyd et al., so that only 1% of the amount of protein inhaled reaches the circulatory system, the dosage delivered by inhalation would still be within the ranges recognized in the art as effective. With the maximum dosages disclosed in Example 8, 0.2 mg (= 200 μg) of FGF and 0.1 mg (= 100 μg) of VEGF would reach the circulatory system. These again are amounts which are significantly above the lowest of the range of dosages disclosed in the art as effective.

Thus, it is respectfully submitted that one skilled in the art would understand that the dosage levels disclosed in the instant specification are indeed within the ranges previously identified for treatment of coronary heart disease by the claimed growth factor proteins.

Moreover, the pulmonary delivery of interferon (another protein of similar molecular weight to the claimed growth factor proteins) is effective, not only as disclosed in the instant specification (see paragraph [0046] at page 19, but also in USP 5,972,331 to Reichert et al. (copy enclosed).

Regarding, delivery of VEGF by IV, this is disclosed, e.g., in paragraph [0006], page 4 of the specification, as well as, for example, in the Freedman et al. and Kurtryk et al. articles that were cited in the Final Rejection.

In summary, it is respectfully submitted that one skilled in the art would be enabled from Applicant's claims to practice the invention of a multi-tiered treatment by inhalation therapy of the claimed proteins. There is more than ample disclosure in Applicant's specification to support such claims.

With regard to the request to perform a literature search for articles directed to inhalation therapy for the claimed growth factor proteins that were published after the effective filing date of the present application, such a search was conducted in the PUBMED database of the National Center for Biotechnology Information (NCBI). However, no relevant article was identified by the search.

In summary, it is respectfully submitted that it has been shown that there is ample enablement of the pending claims and that they fully comply with 35 US 112 ¶1. Accordingly, Applicant respectfully requests that the rejection of the claims on this ground be reconsidered and withdrawn.

Therefore, entry of this Amendment, reconsideration of the rejections and allowance of all of the pending claims (claims 16-19, 21-24, 35-39, 41-43 and 54-61) are most respectfully solicited. Alternatively, entry of this Amendment for purposes of appeal is respectfully requested.

Should any issues remain or should there be any questions, the Examiner is respectfully requested to telephone the undersigned.

Respectfully submitted,
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Enclosures